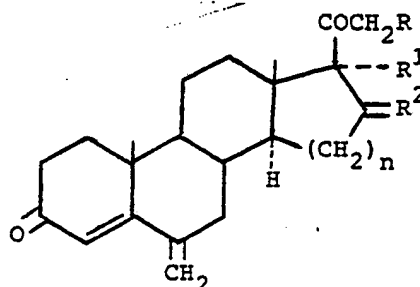
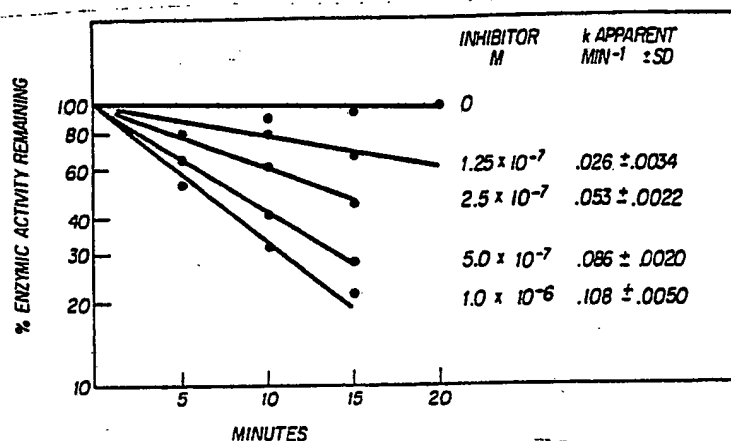


## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/US83/01156 <b>(22) International Filing Date:</b> 29 July 1983 (29.07.83)  <b>(71) Applicant:</b> DUKE UNIVERSITY [US/US]; Durham, NC 27706 (US). <b>(72) Inventors:</b> PETROW, Vladimir ; Route 5, Box 198, Chapel Hill, NC 27514 (US). LACK, Leon ; 2936 Wellcome Drive, Durham, NC 27705 (US). <b>(74) Agents:</b> GUTHRIE, Marvin, C. et al.; Oblon, Fisher, Spivak, McClelland & Maier, Crystal Square Five - Suite 400, 1755 South Jefferson Davis Highway, Arlington, VA 22202 (US).  <b>(81) Designated States:</b> AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK, FR (European patent), GB (European patent), LU (European patent), NL (European patent), SE (European patent).		<b>Published</b> <i>With international search report.</i>

**(54) Title:** METHOD OF TREATING ANDROGEN-RELATED DISORDERS

(I)

**(57) Abstract**

A method of treating androgen-related disorders in an animal which comprises administering to the animal dihydrotestosterone level decreasing amounts of a compound of formula (I), wherein R is H or F; R<sup>1</sup> is selected from the group consisting of -H; straight or branched chain lower alkyl; hydroxyl; -OCOR<sup>3</sup>; and O-(C<sub>1</sub>-C<sub>6</sub> alkyl); wherein R<sup>3</sup> is -H, C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl group, phenyl, phenyl alkylene having straight or branched chain C<sub>1</sub>-C<sub>6</sub> alkylene, C<sub>5</sub>-C<sub>10</sub> cycloalkyl or C<sub>6</sub>-C<sub>10</sub> cycloalkyl alkylene; R<sup>2</sup> is H<sub>2</sub>, methylene, ethylidene, α-CH<sub>3</sub>(H), β-CH<sub>3</sub>(H), α-(OH)(H) or the esteride derived from the 16α, 17α-hydroxy derivative, and n is 1 or 2.

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Description

Method of Treating Androgen-Related Disorders

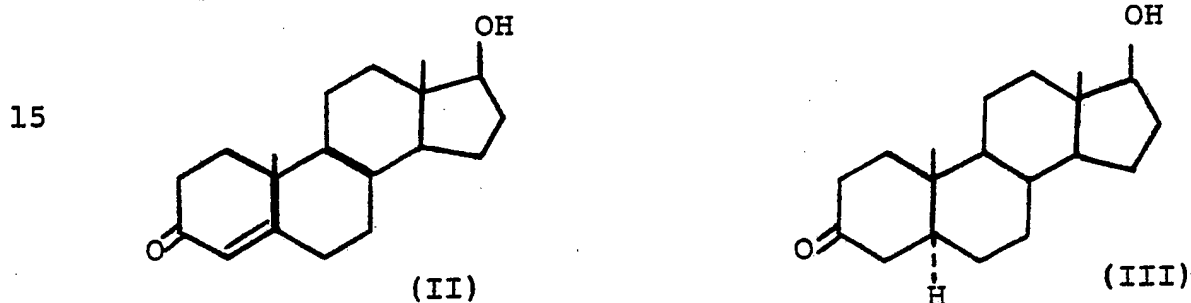
The invention described herein was made in the course of work under a grant or award from the  
5 Department of Health and Human Services.

Technical Field

This invention relates to methods of treating androgen-related disorders and pharmaceutical compositions useful for such treatment.

10 Background Art

Considerable experimental evidence exists supporting the conclusions that the 5 $\alpha$ -reduced metabolite of testosterone (II), 5 $\alpha$ -dihydrotestosterone (III)



is the active form of the androgenic hormone responsible for eliciting somatic androgenic effects, and that testosterone (II) is, de facto, a prohormone [cf. for example, Gloyna, R.E. and Wilson, J.D., J.  
20 Clin. Endocrinol. 29:970(1969); Mainwaring, W.I.P., Mangan, F.R., Wilce, P.A. and Melroy, E.G.P., Advances in Experimental Medicine and Biology, 36:197(1973);

Liao, S., International Review of Cytology,  
41:87(1975)]. It is consequently generally accepted  
that androgen-related disorders stem from excessive  
production of dihydrotestosterone in the body. Such  
5 androgen-related disorders include

acne  
oily skin  
seborrhea  
androgenic alopecia  
10 hirsutism  
androgen-dependent prostatic cancer  
prostatic hypertrophy and virilism.

It follows that treatment, or palliative treatment in  
the case of prostatic carcinoma, of these disorders may  
15 be effected by inhibiting the conversion of (II) into  
(III).

The conversion of testosterone (II) into  
dihydrotestosterone (III) in the body is effected by  
the NADPH-dependent enzyme  $5\alpha$ -reductase. Treatment  
20 of androgen-related disorders may thus be achieved by  
inhibiting the enzyme  $5\alpha$ -reductase. This fact is  
well-documented in the literature (cf. for example,  
U.S.P. 3,917,829; U.S.P. 4,088,760). Progesterone  
appears to be a preferred substrate for the enzyme (cf.  
25 for example, Voight, W., Fernandez, E.P. and Hsia,  
S.L., J. Biol. Chem. 245:5594(1970)), and is well-known  
to be a reversible and competitive inhibitor of the  
enzyme. It is therefore not surprising that  
progesterone has been used to counteract excessive  
30 dihydrotestosterone production. Thus topical  
administration of a 0.5% solution of progesterone in  
aqueous ethanol caused an important decrease in sebum  
secretion in 45/53 males with acne [cf. Vermorken,  
A.J.M. and Jouben, J.J.G., Drug. Intel, Clin. Pharm.,

12:151-157(1978)]. A pro-drug form of progesterone is claimed in Bodor, N.S. and Sloan, K.B., U.S.P. 4,213,978/1980, as useful in the treatment of acne and seborrhea. Progesterone strongly inhibits the enzyme  
5 in cell-culture preparations of human prostate thereby inhibiting growth of the tissue [Sandberg, A., U.I.C.C. Technical Report Series 48:165(1979), see also Massa, R. and Martini, L., Gynec. Invest. 2:253(1971/2)].  
10 Inhibition of the conversion of testosterone to dihydrotestosterone by progesterone in preparations of human benign prostatic hypertrophic tissue has been reported by Tau, S.Y., Antonpillai, I. and Pearson Murphy, B.E. [J. Clin. Endocrinol. Metab. 39:936(1974)]. However, the value of progesterone as  
15 an inhibitor of  $5\alpha$ -reductase, and hence as a therapeutic agent in the treatment of androgen-related disorders, is limited by the following

(i) It is a competitive (reversible) inhibitor of the enzyme. It is now widely recognized that an  
20 irreversible inhibitor offers a distinct advantage over a reversible inhibitor in that it can induce prolonged inactivation of the enzyme and combat the effects of physiological dilution [cf. for example, Shaw, E., in Enzyme Inhibitors as Drugs, Ed. Sandler, M., MacMillan  
25 Press, p. 25, 1980];

(ii) It undergoes metabolism in the body to androstenedione and other androgenic metabolites and is thus unsuitable for systemic administration.

A need therefore exists for progesterone  
30 derivatives which are irreversible inhibitors of the enzyme  $5\alpha$ -reductase..

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Disclosure of the Invention

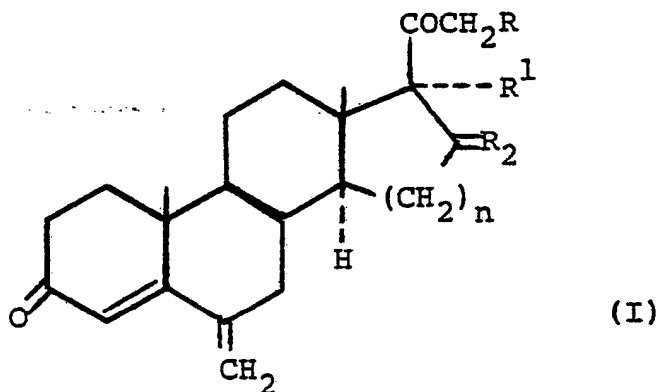
It is therefore an object of the invention to provide a method of treating androgen-related disorders.

5 It is another object of the invention to provide a method as hereinbefore, which utilizes an irreversible inhibitor of the enzyme testosterone -5- $\alpha$ -reductase.

Yet another object of the invention is to provide pharmaceutical compositions for the treatment of  
10 androgen-related disorders.

These and other objects of the invention as will hereinafter become more readily apparent have been attained by providing:

A method for the treatment of androgen-related  
15 disorders in an animal which comprises administering to said animal a compound of the formula (I)



wherein

R is H or F

20 R' is selected from the group consisting of -H; straight or branched chain lower alkyl; hydroxyl; -OCOR<sup>3</sup> and O-(C<sub>1</sub>-C<sub>6</sub> alkyl); wherein R<sup>3</sup> is -H, C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl group, phenyl, phenyl alkylene having straight or branched chain C<sub>1</sub>-C<sub>6</sub>

alkylene, C<sub>5</sub>-C<sub>10</sub> cycloalkyl or C<sub>6</sub>-C<sub>10</sub> cycloalkylalkylene; R<sup>2</sup> is H<sub>2</sub>, methylene, ethylidene, α-CH<sub>3</sub>(H), β-CH<sub>3</sub>(H), α(OH)H, or the acetonide derived from the 16α,17α-dihydroxy derivative, and n is 1 or

5 2.

This invention also relates to pharmaceutical preparations suitable for treating androgen-related disorders.

#### Brief Description of the Drawings

10       FIGURE 1 shows the time course of inactivation of 5α-reductase following incubation of the enzyme with NADPH and 17α-acetoxy-6-methyleneprogesterone; see Example 2.

15       FIGURE 2 demonstrates that the inactivation of the enzyme 5α-reductase follows saturation kinetics, since the plot of the rate constants (as T 1/2 's) versus 1/[Inhibitor] is linear; see Example 2.

#### Best Mode for Carrying Out the Invention

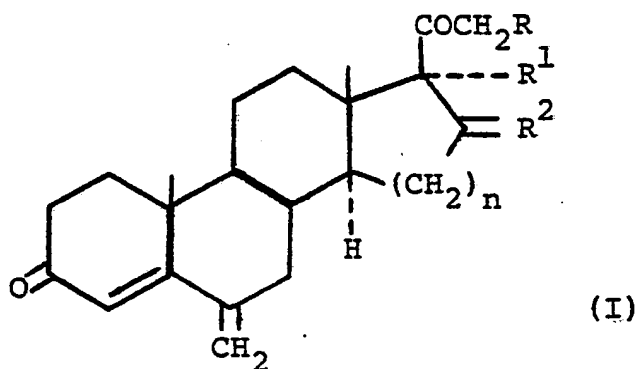
20       As used herein the term androgen-related disorder is intended to mean any disease or condition resulting from overproduction of dihydrotestosterone in the body including acne, oily skin, seborrhea, androgenic alopecia, hirsutism, virilism, androgen-dependent prostatic carcinoma and benign prostatic hypertrophy.

25       For a more detailed description of these conditions, see for example Harrison's Principles of Internal Medicine, 9th Edition, McGraw Hill, 1980, Volume 1, pp. 227-229 (hirsutism, virilism), volume 1,

pages 242-243 (acne), volume 2, pages 1771-1772 (cancer of the prostate), which pages are herein incorporated by reference.

It is the object of this invention to provide  
5 pharmaceutical preparations of the steroids of formula (I) which can be administered to a patient suffering from an androgen-related disorder; this novel method of treatment offers considerable advantages over prior art, for example over estrogen therapy, in that it is  
10 free from deleterious side effects such as estrogenization.

The compounds used in the invention have the formula (I):



15 wherein

R is H or F;

R' is H; lower alkyl containing from 1 or 6 carbon atoms, which may be straight or branched chain such as for example methyl, ethyl, n-propyl, butyl, isobutyl  
20 and the like; hydroxyl; OCOR<sup>3</sup> wherein R<sup>3</sup> may be H, an alkyl moiety containing from 1 to 10 carbon atoms and may be straight or branched chain, such as for example methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, pivalyl, hexyl,  
25 heptyl, octyl and the like; phenyl; phenylalkyl (Ph-alkyl-) wherein the alkyl moiety (which may also be



referred to as an alkylene moiety) has from 1 to 6 carbon atoms and can be straight or branched chain; cycloalkyl wherein the cycloalkyl moiety has from 5 to 10 carbon atoms such as cyclopentyl-, cyclohexyl-, cycloheptyl, cyclooctyl- and their alkylene derivatives containing from 6 to 16 carbon atoms such as cyclopentylmethylene  $C_5H_9CH_2-$ ; O-lower alkyl, wherein the alkyl group has from 1 to 6 carbon atoms and may be straight or branched chain such for example as methyl-, ethyl-, propyl-, iso-propyl-, iso-pentyl, butyl, isobutyl, pentyl;  $R^2$  is  $H_2$ , methylene, ethylidene,  $\alpha$ -Me(H),  $\beta$ -Me(H),  $\alpha$ -(OH)H, and the acetonide derived from the 16 $\alpha$ , 17 $\alpha$ -dihydroxy derivative; n is 1 or 2.

Preferred embodiments of this invention include the following derivatives of 6-Methyleneprogesterone:

- 17 $\alpha$ -acetoxy-
- 17 $\alpha$ -acetoxy-D-homo-
- 17 $\alpha$ -acetoxy-21-fluoro-
- 17 $\alpha$ -acetoxy-21-fluoro-D-homo
- 17 $\alpha$ -caproyloxy-
- 17 $\alpha$ -caproyloxy-D-homo
- 17 $\alpha$ -caproyloxy-21-fluoro-
- 17 $\alpha$ -caproyloxy-21-fluoro-d-homo; the 16 $\alpha$ -methyl-, 16 $\beta$ -methyl- and 16-methylene and ethylidene derivatives of the above (when n = 1),
- 17 $\alpha$ -methyl-
- 17 $\alpha$ -methyl-D-homo-
- 17 $\alpha$ -methyl-21-fluoro-
- 17 $\alpha$ -methyl-21-fluoro-D-homo-; the 17 $\alpha$ -ethyl analogues of the above and their 16 $\alpha$ - and 16 $\beta$ -methyl- derivatives (when n = 1),
- 17 $\alpha$ -methoxy-
- 17 $\alpha$ -methoxy-D-homo

- 17 $\alpha$ -methyl-21-fluoro-  
17 $\alpha$ -methyl-21-fluoro-D-homo-; the 17 $\alpha$ -ethyl  
analogues of the above and their  
16 $\alpha$ - and 16 $\beta$ -methyl-derivatives (when n = 1),
- 5        17 $\alpha$ -methoxy-  
         17 $\alpha$ -methoxy-D-homo-  
         17 $\alpha$ -methoxy-21-fluoro-  
         17 $\alpha$ -methoxy-21-fluoro-D-homo-  
         17 $\alpha$ -ethoxy-  
10       17 $\alpha$ -ethoxy-D-homo-  
         17 $\alpha$ -ethoxy-21-fluoro-  
         17 $\alpha$ -ethoxy-21-fluoro-D-homo-; the 16 $\alpha$ -methyl, 16 $\beta$ -methyl  
         and 16-methylene and ethylidene derivatives of  
         the above (when n = 1)
- 15       acetone from 16 $\alpha$ ,17 $\alpha$ -dihydroxy derivative (when  
         n = 1)
- acetone from the 21-fluoro-16 $\alpha$ ,17 $\alpha$ -dihydroxy  
         derivative (when n = 1) and the D-homo analogs of the  
         above
- 20       6-methylene progesterone and its  
         21-fluoro-  
         16 $\alpha$ -methyl-  
         21- fluoro-16 $\alpha$ -methyl-  
         16 $\beta$ -methyl  
25       21- fluoro-16 $\beta$ -methyl  
         and D-homo analogues of the above.

Most of the compounds claimed in this invention  
are already known in the art. Those that are not known  
can be readily prepared from the known and appropriate  
30 progesterone derivatives by the Vilsmeier or analogous  
processes as reported, for example, in the following  
publications:

- D. Burn et al, Tetrahedron 20:597(1964)  
F. Schneider et al, Helv. Chim. Acta 56:2396(1973)  
M. Muller et al, Helv. Chim. Acta 63:1857(1980)  
D. Burn et al, Tetrahedron 21:569(1965)  
5 D. N. Kirk and V. Petrow, U.S.P. 3,112,305  
F. B. Colton, U.S.P. 2,980,711  
The Upjohn Co. B.P. 1,271,207.

These publications are herein incorporated by reference.

- 10 The compounds employed in the present invention can be administered in various manners to achieve the desired dihydrotestosterone-decreasing effect. The compounds can be administered alone or in the form of pharmaceutical preparations to the patient being  
15 treated orally, parenterally or topically.

- Topical administration is preferred for acne and seborrhea. The amount of compound administered will vary with the severity of the condition being treated. For oral and parenteral administration the  
20 daily dose will generally be from 0.1 to 50 mg/Kg and preferably from 1 to 30 mg/Kg. Unit dosages for oral or parenteral administration may contain, for example, from 5 to 500 mg of the active ingredient.

- For topical administration effective amounts of  
25 the compounds of general formula (I) on a percent basis may vary from 0.001% to 5% and preferably from 0.005% to 1%. For topical administration the formulated active ingredient, that is a compound of general formula I, can be applied directly to the site  
30 requiring treatment or can be applied to the oral or nasal mucosa. Applicator sticks carrying the formulation can be, for example, in the form of a

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solution, suspension, emulsion, gel or cream of either the oil-in-water or water-in-oil type, ointment, paste, jelly, paint or powder. Suitable bases for the topical preparation may be of any conventional type such as

5 oleaginous bases, for example, olive oil, cottonseed oil, petrolatum, white petrolatum, mineral oils, silicones, such as dimethylpolysiloxane, or methylphenylpolysiloxane, lanolins, polyethyleneglycol, glyceryl monostearate, methylcellulose and

10 hydroxymethylcellulose. The topical formulation may contain pharmaceutically acceptable surfactants, wetting agents, dispersing agents, emulsifiers, penetrants, emollients, detergents, hardeners, preservatives, fillers, antioxidants, perfumes, cooling

15 agents, such as menthol, soothing agents, such as camphor, or coloring agents, such as zinc oxide. Aerosol preparations of a solution, suspension or emulsion containing the active ingredient in the form of a finely ground powder can also be employed for

20 topical administration. The aerosol container together with a gaseous or liquified propellant, for example, dichlorofluoromethane, dichlorodifluoromethane with dichlorodifluoroethane, carbon dioxide, nitrogen, or propane with the usual adjuvant such as cosolvent and

25 wetting agents as may be necessary or desirable. The compounds may also be administered in a nonpressurized form such as in a nebulizer or atomizer.

For oral administration the compounds can be formulated into solid or liquid preparations, such as

30 capsules, pills, tablets, troches, powders, solutions, suspensions or emulsions. The compounds can be applied in the form of an aerosol containing finely divided particles of the active ingredient. The solid unit dosage forms can be a capsule which can be of the

ordinary gelatin type containing a compound of general formula I and a carrier, for example, lubricants and inert filler such as lactose, sucrose, and corn starch. In another embodiment the compounds of the  
5 general formula I can be tableted with conventional tablet bases such as lactose, sucrose and corn starch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents such as potato starch or aliginic acids and a lubricant such as stearic acid  
10 or magnesium stearate.

For parenteral administration the compounds may be administered as injectable dosages of a solution or suspension of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which  
15 can be a sterile liquid such a water-in-oil with or without the addition of a surfactant and other pharmaceutically acceptable adjuvants. Illustrative of oils which can be employed in these preparations are those of petroleum, animal, vegetable or synthetic  
20 origin, for example, peanut oil, soybean oil and mineral oil. In general, water, saline, aqueous dextrose and related sugar solutions, ethanols and glycols, such as propylene glycol or polyethylene glycol are preferred liquid carriers, particularly for  
25 injectable solutions.

The compounds can be administered in the form of a depot injection or implant preparation which can be formulated in such a manner as to permit a sustained release of the active ingredient. The active  
30 ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as

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biodegradable polymers and synthetic silicones. For example, Silastic, silicone rubber manufactured by the Dow-Corning Corporation.

The compounds of general Formula I in treating  
5 acne and oily skin conditions may be used in combination with other anti-acne preparations, antiseptics, anti-infective agents, keratolytic agents, for example, benzoic acid, resorcinol or salicylic acid, and comedolytic agents, such as, retinoic acid or  
10 agents having a retinoic acid-like action, corticoids or other antiinflammatory agents, thioglycolates, ethyl lactate or benzoyl peroxide.

In using the products of this invention, topical administration is preferred for acne and seborrhea. The  
15 remaining conditions are preferably treated by systemic administration. In treating benign prostatic hypertrophy and prostatic carcinoma, improved results are obtained by administering the products of the invention concurrently with megestrol acetate,  
20 chlormadinone acetate, medrogestone or cyproterone acetate at therapeutic dose levels.

Having now generally described this invention, the same will be better understood by reference to certain specific examples which are included herein for  
25 purposes of illustration only, and are not intended to be limiting unless otherwise specified.

#### Biological Results

##### Example 1

The compounds of the present invention represent  
30 an important advance over progesterone and derivatives

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thereof since they are irreversible inhibitors of the enzyme 5 $\alpha$ -reductase. Employing the assay of R. J. Moore and J. D. Wilson [Methods in Enzymology, Vol. XXXVI, Academic Press, N.Y., Ed. W. O'Malley and G.

5 Hardman, p. 466-474(1975)], it is found that 6-methyleneprogesterone and

17 $\alpha$ -acetoxy-6-methyleneprogesterone, for example are equipotent with progesterone as inhibitors of the enzyme. On preincubating the enzyme with

10 17 $\alpha$ -acetoxy-6-methyleneprogesterone and NADPH, diluting tenfold and assaying for 5 $\alpha$ -reductase activity, it is surprisingly found, however, that 75% of the enzyme activity is lost. Similar preincubation of the enzyme with progesterone, in striking contrast,  
15 does not result in enzyme inactivation. These results are tabulated below, in Tables 1 and 2.

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**TABLE 1**  
**Effect of Preincubation of Enzyme with 17-Acetoxy-6-methylene-4-pregnen-3,20-dione and NADPH on 5 $\alpha$ -Reductase Activity**

Preincubation conditions Time: 15 min		Enzymic Assay conditions Time: 45 min		Picomol Testosterone reduced/mg protein in 45 min + SEM
Inhibitor	NADPH	Inhibitor	Testosterone	NADPH
M		M		
A	5x10 <sup>-7</sup>	5x10 <sup>-8</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>
B	O	5x10 <sup>-8</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>
C	O	5x10 <sup>-8</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>
D	5x10 <sup>-7</sup>	5x10 <sup>-8</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>
E	No preincubation	O	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>
F	No preincubation	5x10 <sup>-8</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>
				0.71+0.018n = 6
				3.0 +0.26n = 6
				2.83+0.09n = 6
				2.63+0.18n = 6
				4.36+0.24n = 4
				3.14+0.20n = 4

n = number of experiments



**TABLE 2**  
Effect of Preincubation of Enzyme with Progesterone  
and NADPH on 5 $\alpha$ -Reductase Activity

Preincubation conditions Time: 15 min		Conditions during enzymic assay 15 min		Picomol Testosterone Reduced/mg protein in 45 min
Progesterone	NADPH	Progesterone	NADPH	Testosterone
1 0	6x10 <sup>-5</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>	3.91
0	6x10 <sup>-5</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>	3.41
2 5x10 <sup>-7</sup>	6x10 <sup>-5</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>	3.91
5x10 <sup>-7</sup>	6x10 <sup>-5</sup>	5x10 <sup>-8</sup>	5x10 <sup>-4</sup>	3.79
3 No preincubation		0	5x10 <sup>-4</sup>	5.80
No preincubation		0	5x10 <sup>-4</sup>	5.42
4 No preincubation		5x10 <sup>-8</sup>	5x10 <sup>-4</sup>	3.66
No preincubation		5x10 <sup>-8</sup>	5x10 <sup>-4</sup>	5.54

These observations reveal that  
17 $\alpha$ -acetoxy-6-methyleneprogesterone, in striking  
contrast to progesterone, combines with the enzyme in  
the presence of the co-factor NADPH in an irreversible  
5 manner, whilst progesterone inactivation of the enzyme  
is competitive and reversible.

### Example 2

The time course of inactivation of 5 $\alpha$ -reductase  
following incubation of the enzyme with NADPH and  
10 17 $\alpha$ -acetoxy-6-methyleneprogesterone is shown in Fig.  
1.

This time course of inactivation of the enzyme can  
be seen to follow pseudo first-order kinetics, which is  
in accord with the postulate that the inhibition  
15 invoked by such preincubation exposure is  
irreversible. When these rate constants are plotted  
(as the  $t_{1/2}$  's) against the reciprocal of the  
inhibitor concentrations, a straight line is obtained  
with a positive intercept on the y-axis, indicating a  
20 saturation phenomenon (Fig. 2). These data are in  
accord with the conclusion that the interaction of the  
inhibitor with the enzyme shows two phases. The first  
is a reversible combination of the enzyme and inhibitor  
with a  $K_i$  of  $1.25 \times 10^{-6}$ M. The enzyme-inhibitor  
25 complex then undergoes irreversible combination  
rendering the enzyme inactive. The rate constant for  
this step ( $k_{cat}$ ) is  $4.8 \times 10^{-3} \text{ sec}^{-1}$ .

### Formulations

Following are illustrative topical pharmaceutical  
30 formulations which may be employed in practicing the

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present invention:

Example 3

Solution

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	0.85 g
5	Alcohol	78.9 ml
	Isopropyl Myristate	5.0 g
	Polyethylene Glycol 400	10.0 g
	Purified Water qs ad	100. ml

Combine the alcohol, isopropyl myristate and  
10 polyethylene glycol 400 and dissolve the drug substance  
therein. Add sufficient purified water to give 100 ml.

Example 4

A Gel

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	0.85 g
15	Alcohol	78.9 ml
	Isopropyl Myristate	5.0 g
	Polyethylene Glycol 400	10.0 g
	Carbopol 940 (Carboxypolymethylene)	0.75 g
	Triethylamine	. qs
20	Purified Water qs ad	85. g

Disperse the Carbopol 940 in the isopropyl myristate.  
To 38 ml of alcohol add 7 ml of purified water and the  
polyethylene glycol 400 and mix. Combine the two  
phases and mix until well dispersed. Add sufficient  
25 triethylamine to give a neutral pH. Dissolve the drug  
substance in the balance of the alcohol and mix well  
into the batch. Add and mix sufficiently purified

water to provide 85 g of finished product.

Example 5

Applicator Stick

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	0.85 g
5	Absolute Alcohol	75. ml
	Polyethylene Glycol 400	10.0 g
	Isopropyl Myristate	5.0 g
	Stearic Acid	4.3 g
	Sodium Hydroxide	0.55 g
10	Purified Water qs ad	85. g

Combine the absolute alcohol, polyethylene glycol 400 and isopropyl myristate and dissolve the drug substance therein. Add the stearic acid and heat the mixture to about 65°C. Dissolve the sodium hydroxide in a small amount of water, add and mix. Add sufficient water to provide 85 g of finished product. Pour into suitable molds and allow to solidify.

Example 6

Aerosol Foam

20	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1.0 g
	Propylene Glycol	96.0 g
	Emulsifying Wax NF XIV	3.0 g
	Dichlorodifluoromethane: cryofluorane (20:80)	6.9 g

25 Dissolve the drug substance in the propylene glycol. Add the emulsifying wax and heat to approximately 70°C. Stir while cooling to room temperature. Charge a suitable aerosol unit with this concentrate and 6.9 g of dichlorodifluoromethane: cryofluorane (20:80).

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Example 7

Topical Cream, Vanishing, o/w

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1.
	Stearic Acid	15.
5	Sorbitan Monostearate	2.
	Polyoxyethylene Sorbitan Monostearate	2.3
	Propylene Glycol	5.
	Methylparaben	0.025%
	Propylparaben	0.015%
10	Purified Water	qs

Example 8

Buccal or Sublingual Tablet

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1%
	Calcium Stearate	1%
15	Calcium Saccharin	0.02%
	Granular Mannitol	qs

Mix and compress on a suitable tablet machine to a weight of 0.115 g/tablet.

Example 9

Powder

20	17 $\alpha$ -Acetoxy-6-methyleneprogesterone, micronized	1
	Silicone dioxide, anhydrous	0.5
	Corn starch, lactose, fine powder aa	qs

Example 10

Oleaginous Ointment

25	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1
	White wax	5
	White petrolatum qs	100

Example 11

Absorption Ointment Base

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1
	Cholesterol	3
5	Stearyl alcohol	3
	White wax	8
	White petrolatum qs	100

Example 12

Water Soluble Ointment Base

10	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1
	Polyethylene glycol 4000	40
	Polyethylene glycol 400 qs	100

Example 13

Paste

15	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1
	Starch	25
	Zinc oxide	25
	White petrolatum qs	100

Example 14

Aerosol Foam

20	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1
	Emulsifying wax	3
	Stearic acid	1
	Stearyl alcohol	1
25	Diglycol stearate	2
	Propylene glycol	92

The following are illustrative pharmaceutical formulations suitable for oral or parenteral administration which may be employed in practicing the present invention:

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Example 15

Tablet

For 15,000

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	75. g
	Lactose	1.216 Kg
5	Corn Starch	0.3 Kg

Mix the active ingredient, the lactose and corn starch uniformly. Granulate with 10% starch paste. Dry to a moisture content of about 2.5%. Screen through a No. 12 mesh screen. Add and mix the following:

10	Magnesium Stearate	0.015 Kg
	Corn Starch qs ad	1.725 Kg

Compress on a suitable tablet machine to a weight to 0.115 g/tablet.

Example 16

15 Soft Gelatin Capsule

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	0.25 Kg
	Polysorbate 80	0.25 Kg
	Corn Oil qs ad	25.0 Kg

Mix and fill into 50,000 soft gelatin capsules.

20

Example 17

IM Depot Injection

Each 1 ml contains the following:

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	5.0 mg
	Anhydrous Chlorobutanol	5.0 mg
25	Aluminum Monostearate	50.0 mg
	Peanut Oil qs ad	1.0 ml

Dissolve or disperse the ingredients in the peanut oil.

Example 18

Depot-Implant

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	5.0 mg
	Anhydrous Chlorobutanol	5.0 mg
5	Aluminum Monostearate	50.0 mg
	Peanut Oil qs ad	1.0 ml

Dissolve or disperse the ingredients in the peanut oil.

Example 18

Depot-Implant

10	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	5. mg
	Dimethylsiloxane	240. mg
	Catalyst qs	

Disperse the drug substance in the fluid  
dimethylsiloxane. Add the catalyst and cast into a  
15 suitable monolytic structure.

Alternatively, the drug substance may be enclosed  
by a precast polydimethylsiloxane envelope.

Alternatively, the drug substance may be dispersed  
in a suitable amount of hydroxyethyl acrylate  
20 subsequently polymerized and cross-linked by the  
addition of ethylenedimethacrylate, and an oxidizing  
agent, to yield a 3-dimensional ethylene  
glycomethacrylate mouldable gel (Hydron).

Example 19

IM Injections

25

A. Oil Type:

	17 $\alpha$ -Acetoxy-6-methyleneprogesterone	25. mg
	BHA, BHT aa	0.01% w/v
	Peanut Oil or Sesame Oil qs	1.0 ml

30 B. Suspension Type



17 $\alpha$ -Acetoxy-6-methyleneprogesterone	25. mg
Sodium Carboxymethylcellulose	0.5% w/v
Sodium Bisulfite	0.02% w/v
Water for Injection, qs	1.0 ml

5

Example 20

Buccal or Sublingual Tablet

17 $\alpha$ -Acetoxy-6-methyleneprogesterone	1%
Calcium Stearate	1%
Calcium Saccharin	0.02%
Granular Mannitol	qs

Mix and compress on a suitable tablet machine to a weight of 0.115 g/tablet.

The following formulations are illustrative of pharmaceutical preparations for topical application comprising a compound of general Formula I in combination with a keratolytic agent.

Example 21

Aerosol Foam

		% w/w
17 $\alpha$ -Acetoxy-6-methyleneprogesterone	0.85	g
Resorcinol	0.85	g
Alcohol	78.9	ml
Isopropyl myristate	5.0	g
Polyethylene glycol 400	10.0	g
Carbopol 940 (carboxypolymethylene)	0.75	g
Triethylamine	qs	
Purified water qs ad		

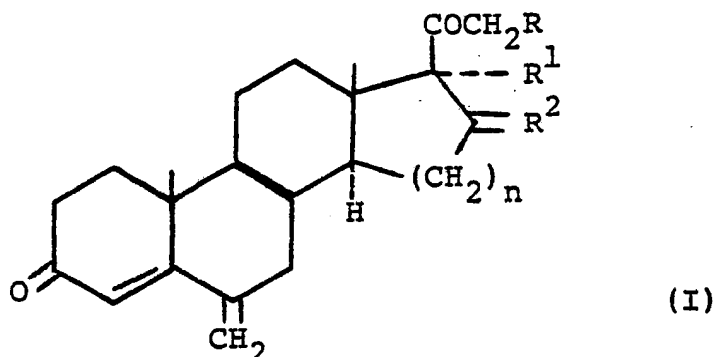
Disperse the Carbopol 940 in the isopropyl myristate. To 38 ml of alcohol add 7 ml of purified water and the polyethylene glycol 400 and mix. Combine the two phases and mix until well dispersed. Add sufficient

triethylamine to give a neutral pH. Dissolve the drug substance and the resorcinol in the balance of the alcohol and mix well into the batch. Add and mix sufficient purified water to provide 85 g of finished product.

Having now fully described this invention, it will be understood that the same can be practiced within a wide range of equivalent composition and administration values without affecting the scope or spirit of the invention or any embodiment thereof.

Claims

1. A method of treating androgen-related disorders in an animal which comprises administering to said animal dihydrotestosterone level decreasing amounts of a compound of formula (I):



wherein R is H or F;

- R<sup>1</sup> is selected from the group consisting of -H; straight or branched chain lower alkyl; hydroxyl; -OCOR<sup>3</sup>; and O-(C<sub>1</sub>-C<sub>6</sub> alkyl); wherein R<sup>3</sup> is -H, C<sub>1</sub>-C<sub>10</sub> straight or branched chain alkyl group, phenyl, phenyl alkylene having straight or branched chain C<sub>1</sub>-C<sub>6</sub> alkylene; C<sub>5</sub>-C<sub>10</sub> cycloalkyl or C<sub>6</sub>-C<sub>10</sub> cycloalkyl alkylene; R<sup>2</sup> is H<sub>2</sub>, methylene, ethylidene, α-CH<sub>3</sub>(H), β-CH<sub>3</sub>(H)<sub>m</sub> α-(OH)<sub>h</sub> or the acetonide derived from the 16α, 17α -dihydroxy derivative, and n is 1 or 2.

2. The method of Claim 1 wherein the androgen-related disorder is selected from the group consisting of acne, seborrhea, and androgenic alopecia.
3. The method of Claim 2 wherein the compound is administered as a topical preparation containing from 0.001% to 5% of the compound.
4. The method of Claim 1 wherein the androgen-

related disorder is selected from the group consisting of oily skin, hirsutism, benign prostatic hypertrophy and androgen dependent prostatic adenocarcinoma.

5        5. The method of Claim 4 wherein the compound is administered orally in an amount of from 0.1 to 50 mg/Kg.

6. The method of Claim 4 where the compound is administered parenterally in an amount of from 0.1 to 50 mg/Kg.

10       7. The method of Claim 4 wherein said disorder is androgen dependent prostatic adenocarcinoma and the compound is administered together with a compound selected from the group consisting of megestrol acetate medrogestone and cyproterone acetate.

15       8. The method of Claim 1 wherein  $R=R^1=H$ ,  $R^2$  is  $=H_2$  and  $n=1$ .

9. The method of Claim 1 wherein  $R=H$ ,  $R^1=OAc$ ,  $R^2$  is  $=H_2$  and  $n=1$ .

20       10. The method of Claim 1 wherein  $R=H$ ,  $R^1=OAc$ ,  $R^2$  is  $=CH_2$  and  $n=1$ .

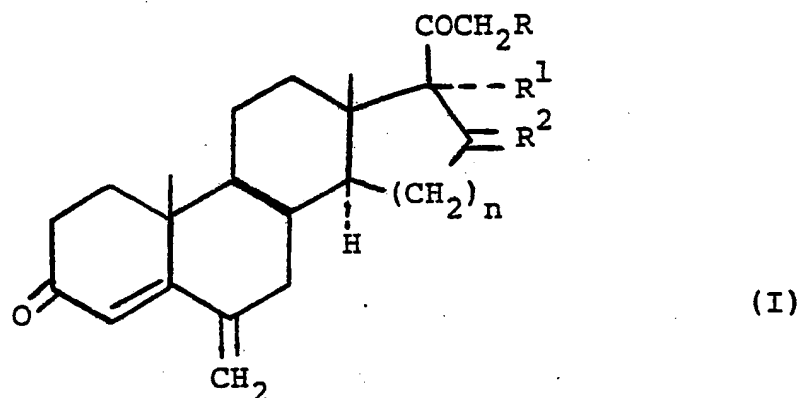
11. The method of Claim 1 wherein  $R=H$ ,  $R^1=OAc$ ,  $R^2$  is  $\alpha\text{-Me(H)}$  and  $n=1$ .

12. The method of Claim 1 wherein  $R=H$ ,  $R^1=OAc$ ,  $R^2$  is  $\beta\text{-Me(H)}$  and  $n=1$ .

25       13. The method of Claim 1 wherein  $R=H$ ,  $R^1=OAc$ ,  $R^2$  is  $=H_2$  and  $n=2$ .

14. The method of Claim 1 wherein  $R=R^1=H$ ,  $R^2$  is  $=H_2$  and  $n=2$ .

15. A pharmaceutical composition for topical application to the skin of a patient suffering from an androgen-related disorder which comprises  $5\alpha$ -dihydrotestosterone level decreasing amount of a compound of the formula:



wherein

- 10 R is H or F;  
 $R^1$  is selected from the group consisting of -H;  
 straight or branched chain lower alkyl; hydroxyl;  
 $-OCOR^3$  and  $O-(C_1-C_6 \text{ alkyl})$ ; wherein  $R^3$  is -H,  $C_1-C_{10}$   
 straight or branched chain alkyl group, phenyl, phenyl  
 15 alkylene having straight or branched chain  $C_1-C_{10}$   
 straight or branched chain alkyl group, phenyl, phenyl  
 alkylene having straight or branched chain  $C_1-C_6$   
 alkylene,  $C_5-C_{10}$  cycloalkyl or  $C_6-C_{10}$  cycloalkyl  
 alkylene;  $R^2$  is  $H_2$ , methylene, ethylidene,  
 20  $\alpha-CH_3(H)$ ,  $\beta-CH_3(H)$ ,  $\alpha(OH)$  (H) or the acetonide derived  
 from the  $16\alpha,17\alpha$ -dihydroxy derivative, and  $n$  is 1 or 2;  
 together with an inert topical pharmaceutical carrier.

16. The composition of Claim 15 where said carrier is selected from oleaginous bases, silicones, lanolines, polyethylene glycol, glyceryl monostearate, methylcellulose and hydroxymethylcellulose.

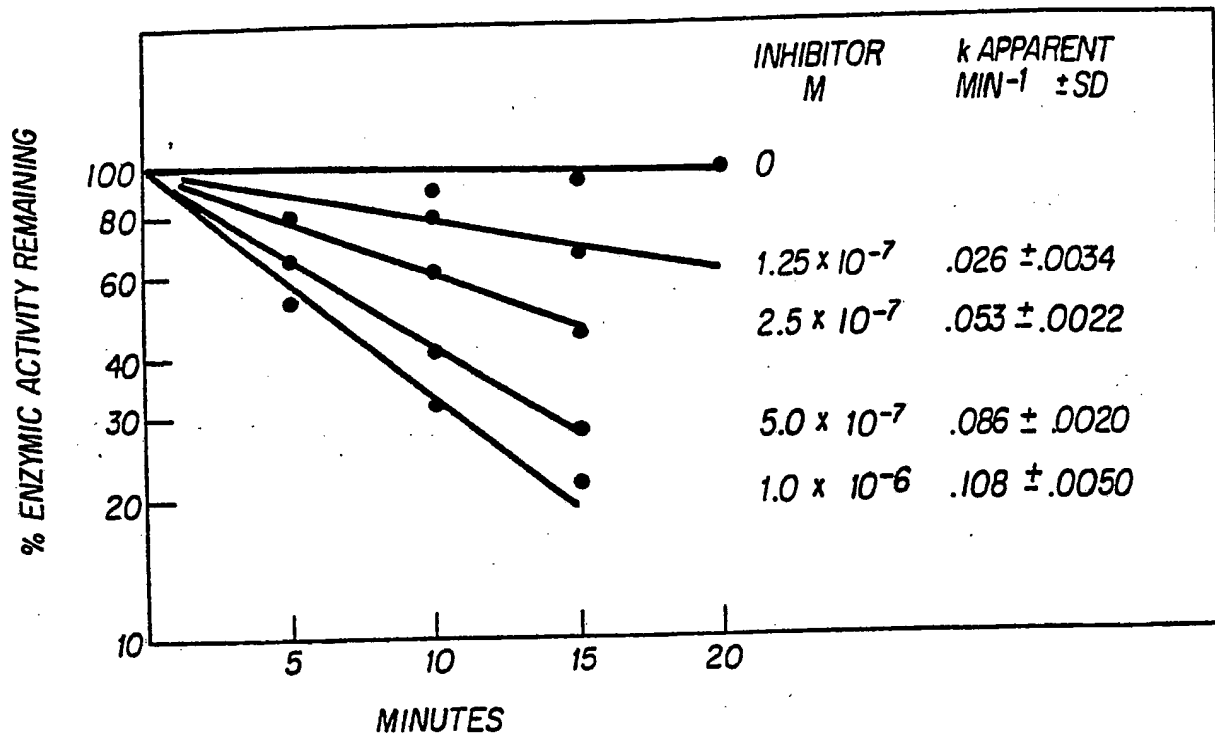


FIG. 1

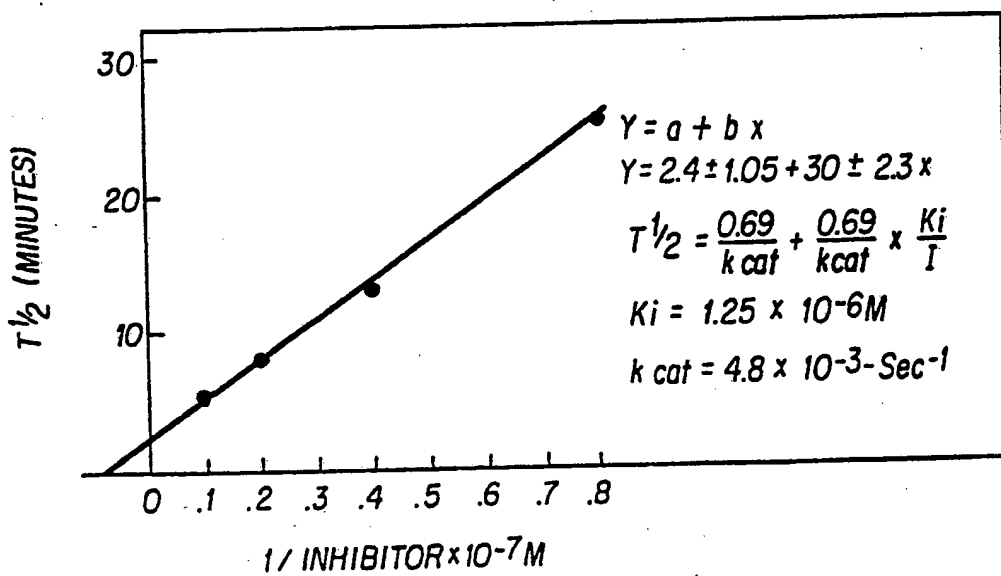


FIG. 2

# INTERNATIONAL SEARCH REPORT

International Application No **PCT/US83/01156**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>3</sup> According to International Patent Classification (IPC) or to both National Classification and IPC <b>3</b> <b>A61K 31/56</b> <b>424/242</b>								
<b>II. FIELDS SEARCHED</b> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Minimum Documentation Searched <sup>4</sup></div> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 20%; border-bottom: 1px solid black;">Classification System</th> <th style="border-bottom: 1px solid black;">Classification Symbols</th> </tr> <tr> <td style="border-right: 1px solid black; text-align: center; padding: 5px;">U.S.</td> <td style="padding: 5px;">424/242; 260/397.3</td> </tr> </table> <div style="text-align: center; border-top: 1px solid black; border-bottom: 1px solid black;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>5</sup></div> <p style="padding: 5px;">Chemical Abstracts: 1946 to date "6-methylene-Progesterone-uses"</p>			Classification System	Classification Symbols	U.S.	424/242; 260/397.3		
Classification System	Classification Symbols							
U.S.	424/242; 260/397.3							
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup> <table style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%; border-bottom: 1px solid black;">Category <sup>8</sup></th> <th style="border-bottom: 1px solid black;">Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup></th> <th style="width: 10%; border-bottom: 1px solid black;">Relevant to Claim No. <sup>18</sup></th> </tr> <tr> <td style="border-right: 1px solid black; text-align: center; vertical-align: top; padding: 10px;">A</td> <td style="border-right: 1px solid black; padding: 10px;">US, A, 4,055,641, published October 1977 Benson et al.</td> <td style="padding: 10px;"></td> </tr> </table>			Category <sup>8</sup>	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>	A	US, A, 4,055,641, published October 1977 Benson et al.	
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<table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <ul style="list-style-type: none"> <li>* Special categories of cited documents: <sup>15</sup></li> <li>"A" document defining the general state of the art which is not considered to be of particular relevance</li> <li>"E" earlier document but published on or after the international filing date</li> <li>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</li> <li>"O" document referring to an oral disclosure, use, exhibition or other means</li> <li>"P" document published prior to the international filing date but later than the priority date claimed</li> </ul> </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <ul style="list-style-type: none"> <li>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</li> <li>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</li> <li>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</li> <li>"G" document member of the same patent family</li> </ul> </td> </tr> </table>			<ul style="list-style-type: none"> <li>* Special categories of cited documents: <sup>15</sup></li> <li>"A" document defining the general state of the art which is not considered to be of particular relevance</li> <li>"E" earlier document but published on or after the international filing date</li> <li>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</li> <li>"O" document referring to an oral disclosure, use, exhibition or other means</li> <li>"P" document published prior to the international filing date but later than the priority date claimed</li> </ul>	<ul style="list-style-type: none"> <li>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</li> <li>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</li> <li>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</li> <li>"G" document member of the same patent family</li> </ul>				
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<b>IV. CERTIFICATION</b> <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border-right: 1px solid black; padding: 5px;">           Date of the Actual Completion of the International Search <sup>2</sup>  <div style="text-align: center; font-size: 1.2em;">October 10, 1983</div> </td> <td style="width: 50%; padding: 5px;">           Date of Mailing of this International Search Report <sup>3</sup>  <div style="text-align: center; font-size: 1.2em;">24 OCT 1983</div> </td> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px;">           International Searching Authority <sup>1</sup>  <div style="text-align: center; font-size: 1.2em;">ISA/US</div> </td> <td style="padding: 5px;">           Signature of Authorized Officer <sup>19</sup>  <div style="text-align: center;">              Elbert L. Roberts           </div> </td> </tr> </table>			Date of the Actual Completion of the International Search <sup>2</sup> <div style="text-align: center; font-size: 1.2em;">October 10, 1983</div>	Date of Mailing of this International Search Report <sup>3</sup> <div style="text-align: center; font-size: 1.2em;">24 OCT 1983</div>	International Searching Authority <sup>1</sup> <div style="text-align: center; font-size: 1.2em;">ISA/US</div>	Signature of Authorized Officer <sup>19</sup> <div style="text-align: center;">              Elbert L. Roberts           </div>		
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